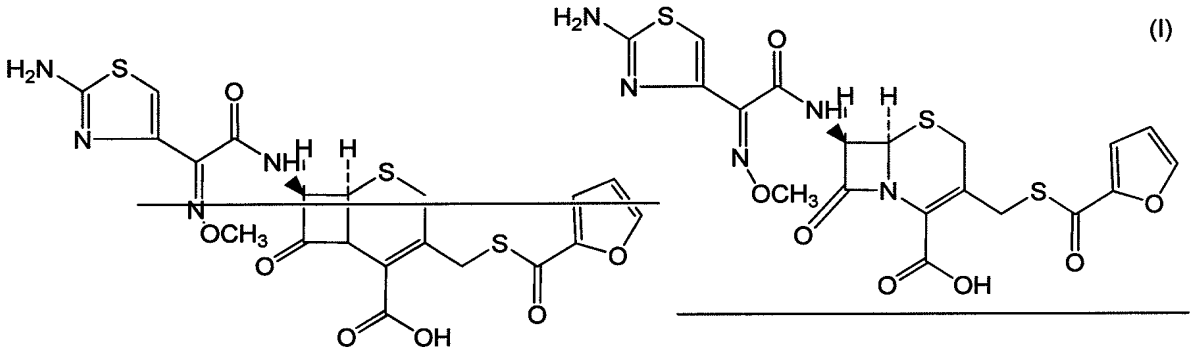
IN THE SPECIFICATION

Page 1, paragraph [0002], replace with

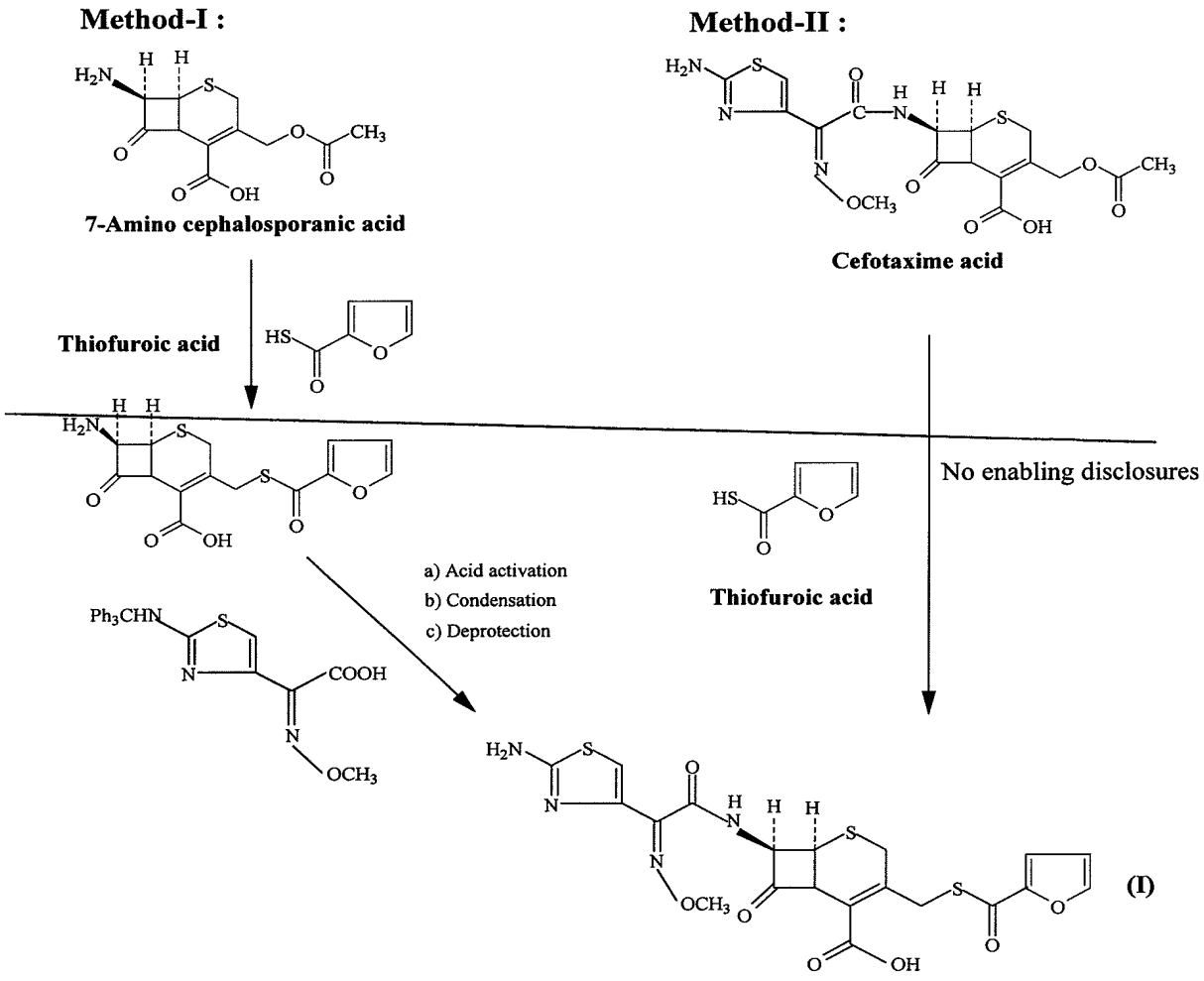
Ceftiofur is a broad-spectrum third generation antibiotic, which is primarily used for veterinary use. It is known chemically as (6R, 7R)-7-[[(2Z)-(2-amino-4-thiazolyl) (methoxyimino) acetyl]amino]-3-[[(2-furanylcarbonyl) thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid and is represented by the formula (I).



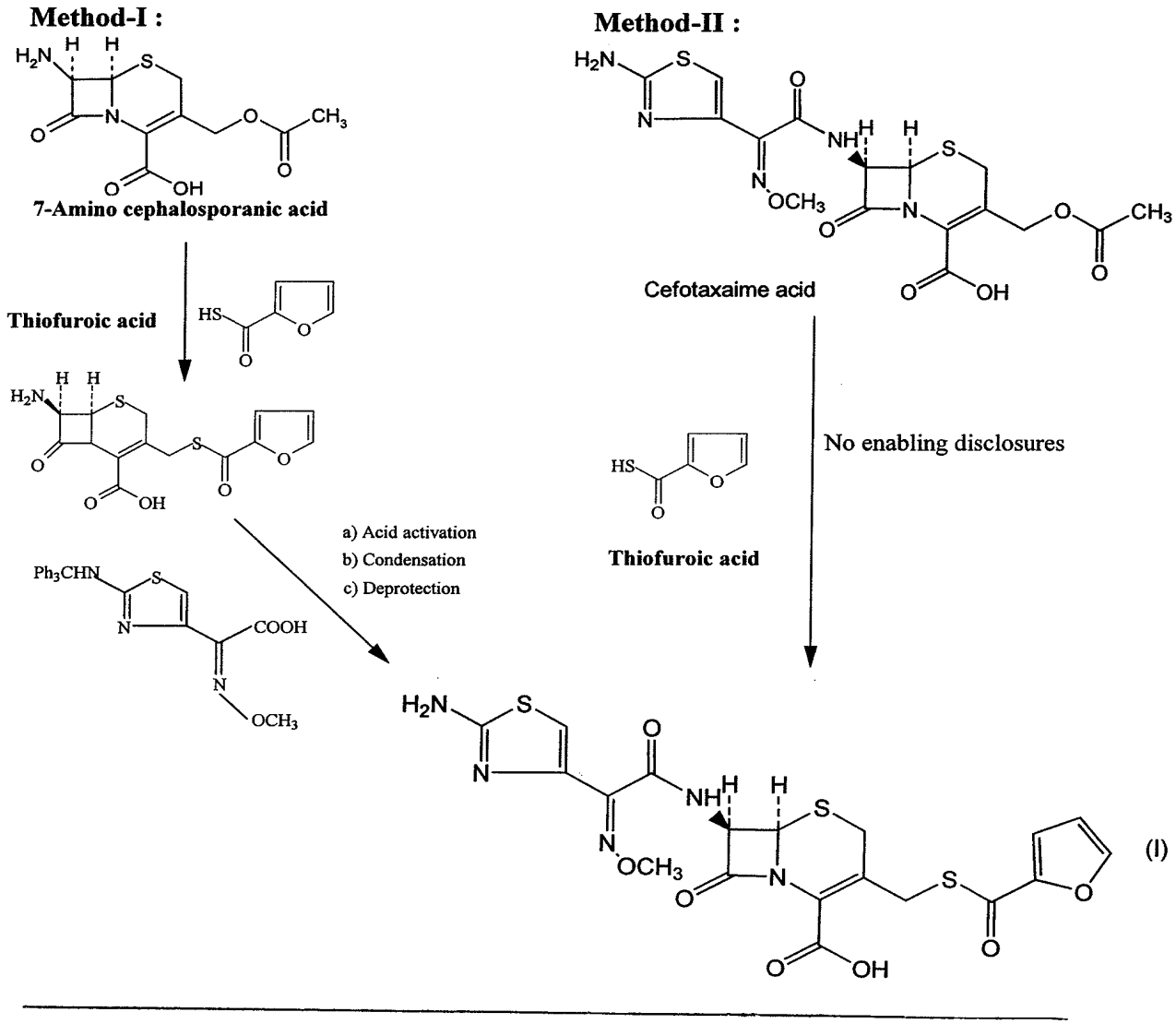
(I)

Page 2, replace scheme (I) with the following:

Scheme I: Method for preparation of ceftiofur (I) as disclosed in US. Pat. No. 4.464,367

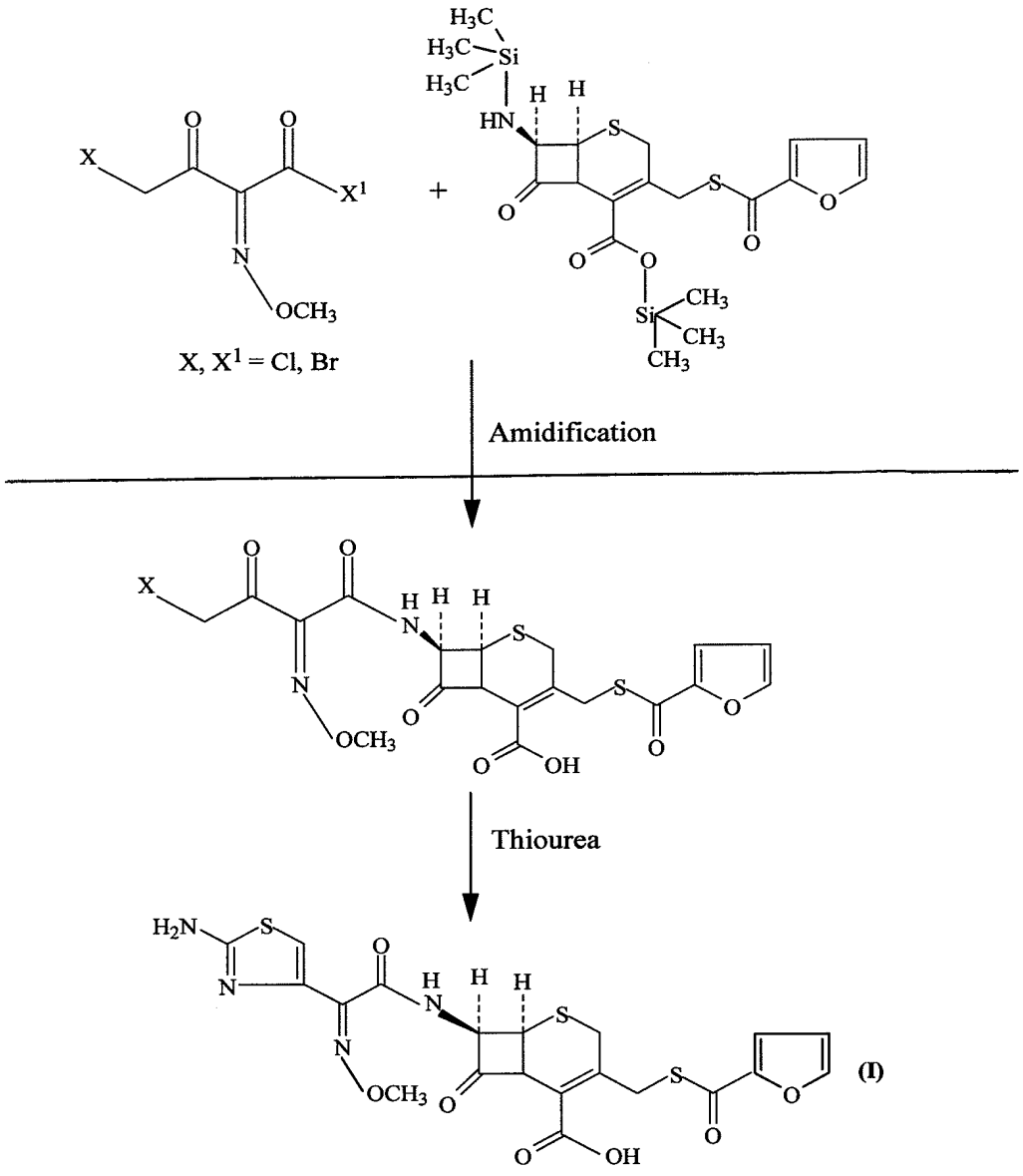


Scheme I: Method for preparation of ceftiofur (I) as disclosed in US. Pat. No. 4.464,367

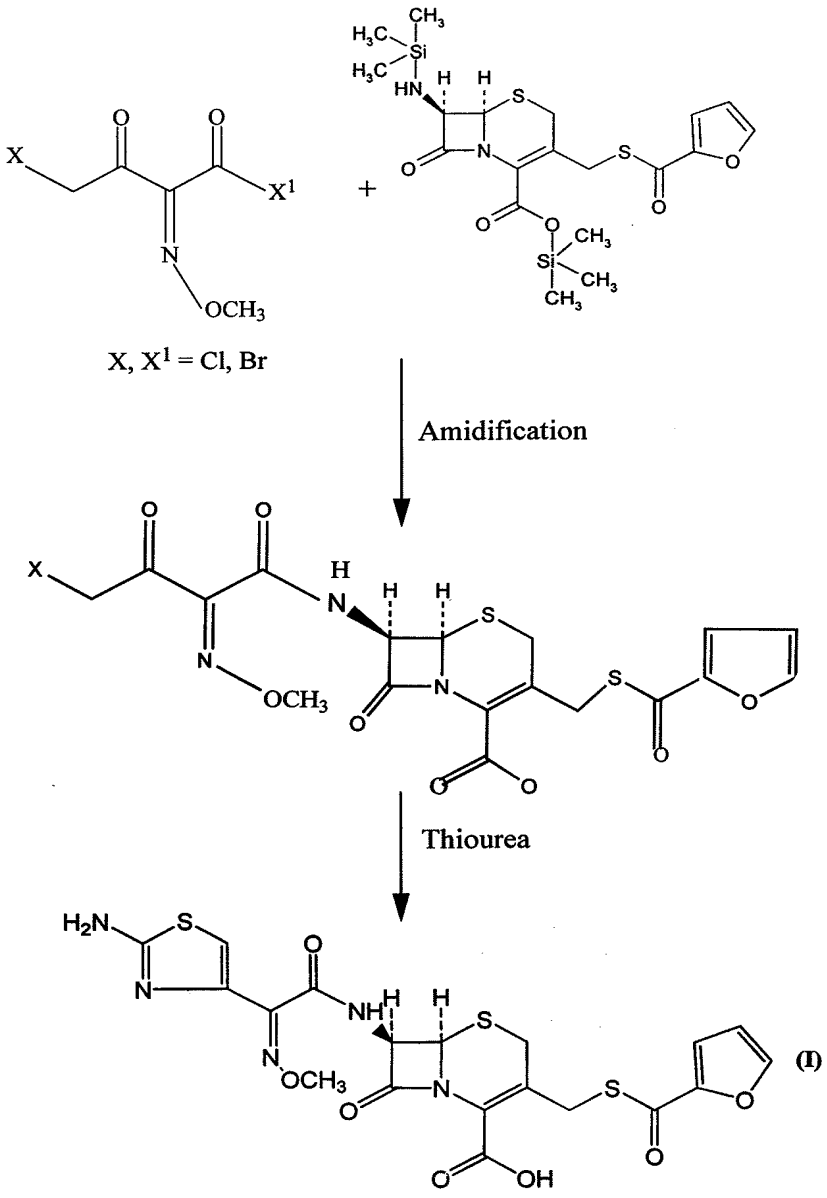


Page 3, replace scheme (II) with the following:

Scheme II: Method for preparation (I) as disclosed in US. Pat. No. 6,458,949 B1

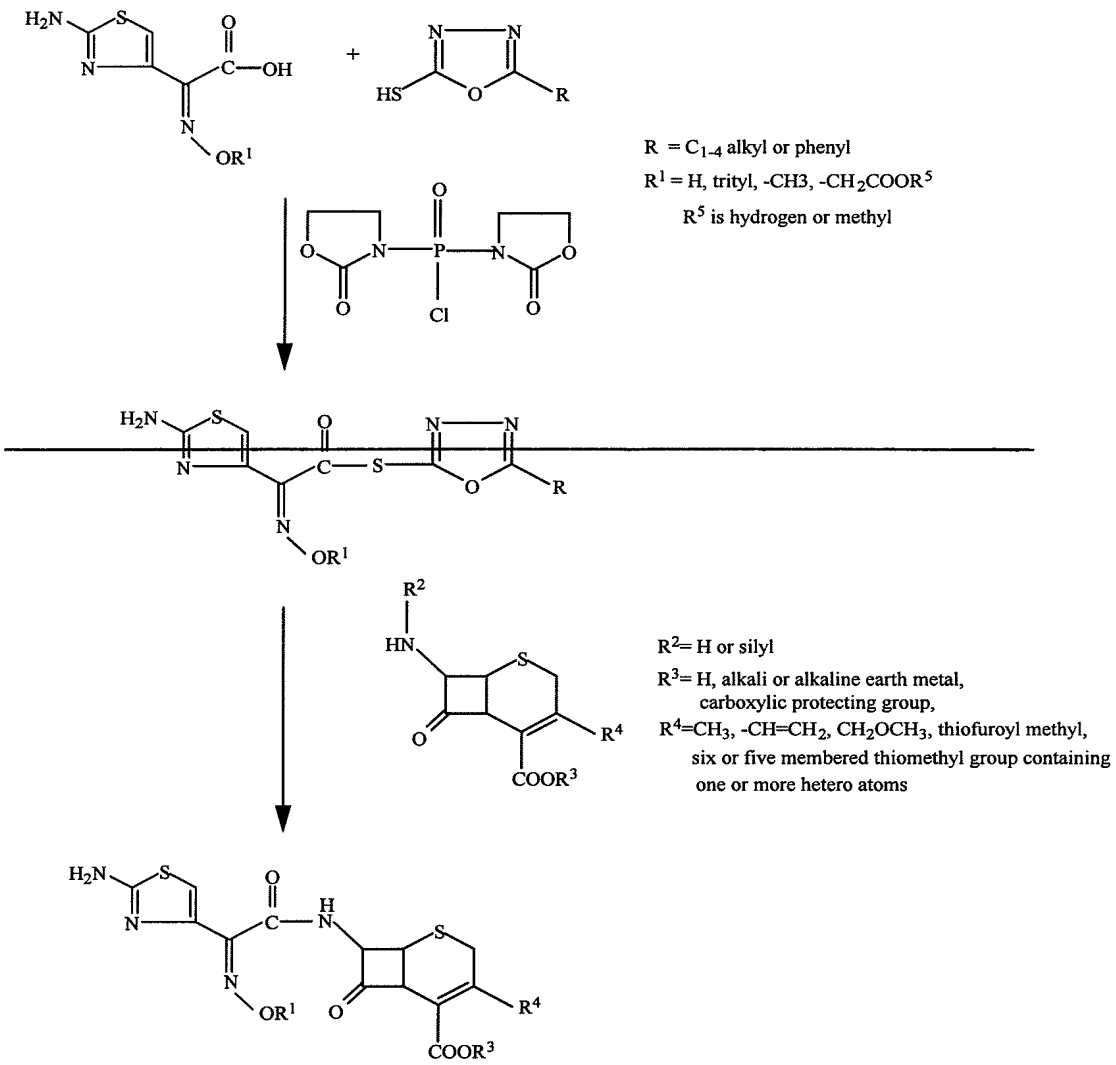


Scheme II: Method for preparation (I) as disclosed in US. Pat. No. 6,458,949 B1

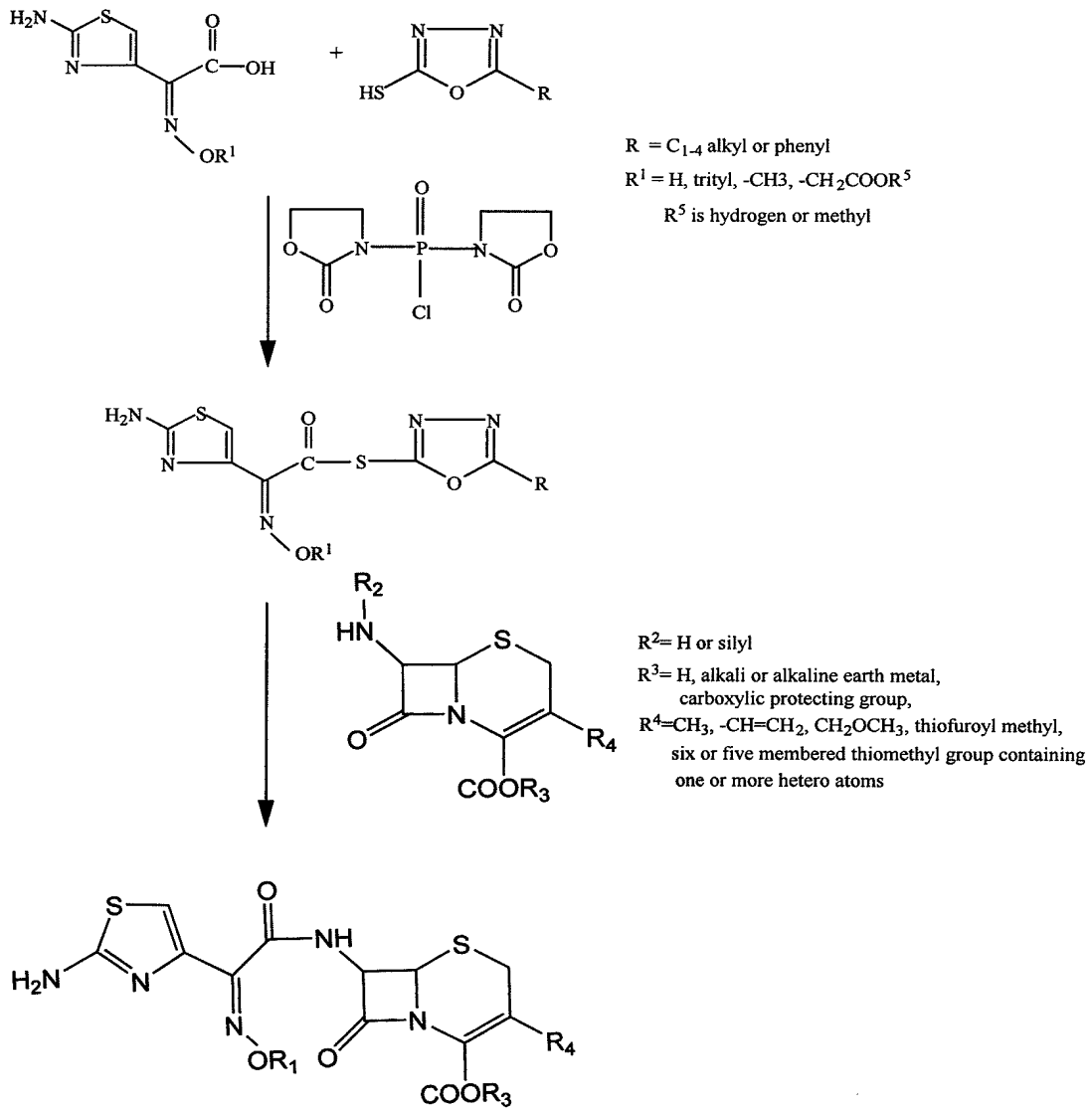


Page 4, replace scheme (III) with the following:

Scheme III: Method for preparation (I) as disclosed in US Pat. No. 6,388,070 B1



Scheme III: Method for preparation (I) as disclosed in US Pat. No. 6,388,070 B1



$R = C_{1-4}$ alkyl or phenyl

R^1 = H, trityl, -CH3, $-CH_2COOR^5$

R^5 is hydrogen or methyl

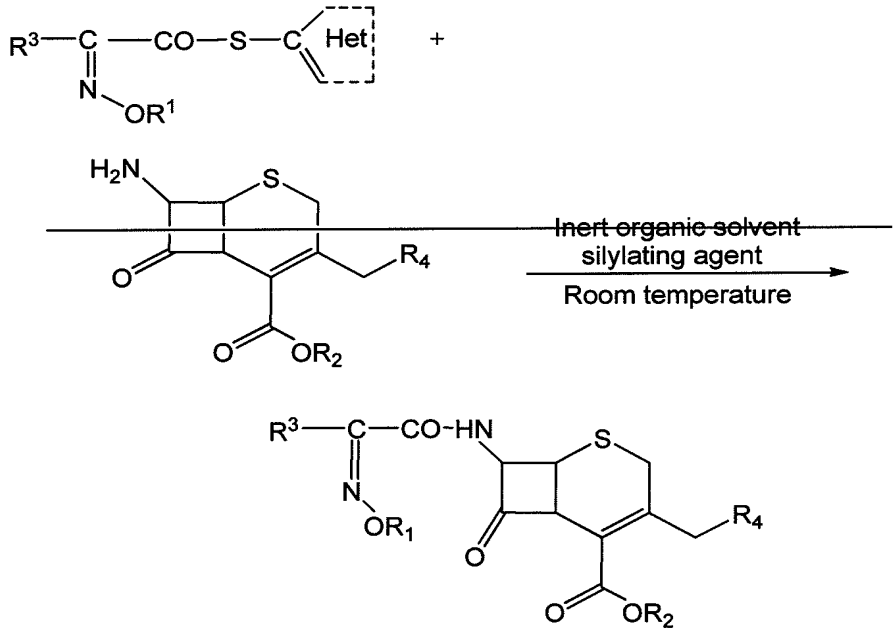
R^2= H or silyl

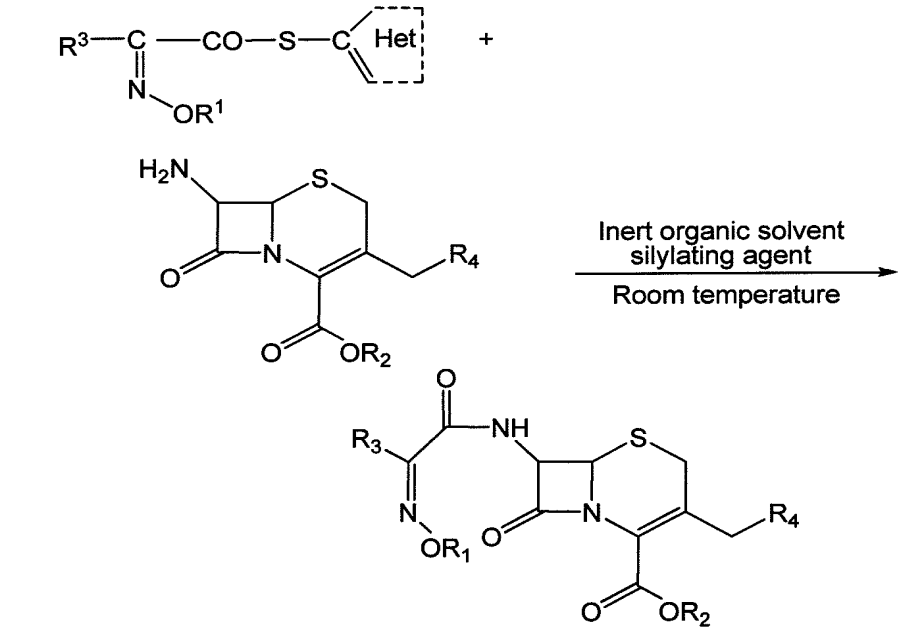
R^3= H, alkali or alkaline earth metal, carboxylic protecting group,

R^4=CH_3, $-CH=CH_2$, CH_2OCH_3, thiofuroyl methyl, six or five membered thiomethyl group containing one or more hetero atoms

Page 5, replace paragraph [0024] with:

A reactive derivative of [(2)-(2-aminothiazol-4-yl)]-2-syn-oxyimino acetic acid compounds widely utilized in cephalosporin chemistry for effecting amidification at 7-position is the 2-benzothiazolyl thioester, first disclosed in US Patent No. 4,767,852 (Ascher et. al), the chemistry of which is shown hereinbelow.

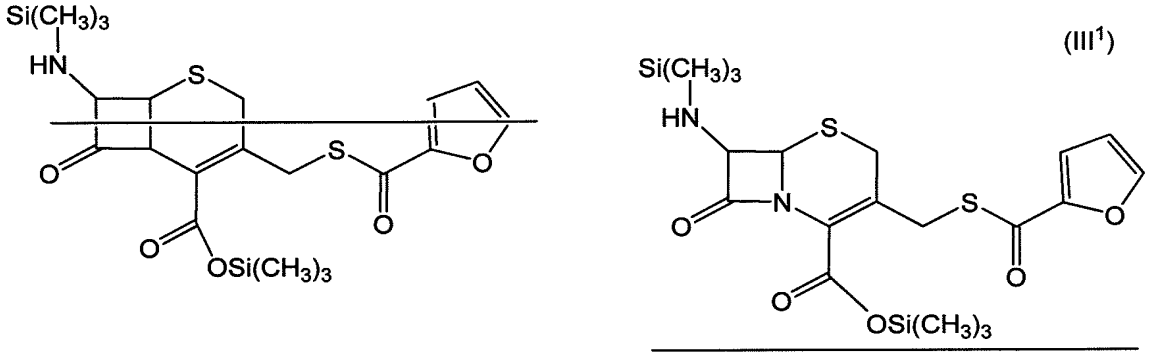




wherein the groups R^1 to R^3 are as defined therein and the group R^4 is an acetoxy, carbamoyloxy, or is a group of formula S-Y, wherein Y is a heterocyclic ring.

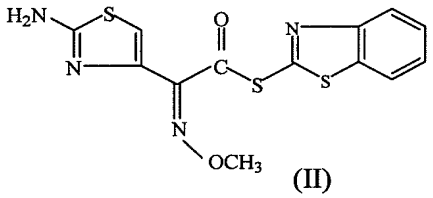
Page 5, replace the formulas in paragraph [0031] with:

In their attempt to extend the method described in US Patent No. 4,767,852 and US Patent No. 6,313,289, for synthesis of ceftiofur the present inventors found to their surprise that when (N,O)-bis silyl-7-amino-3-thiofuroylmethyl-3-cephalosporanic acid of formula (III^1),



is reacted with [2-(2-aminothiazol-4-yl)]-2-methoxyimino acetic acid-2-benzothiazolyl

thioester (MAEM) of formula (II),

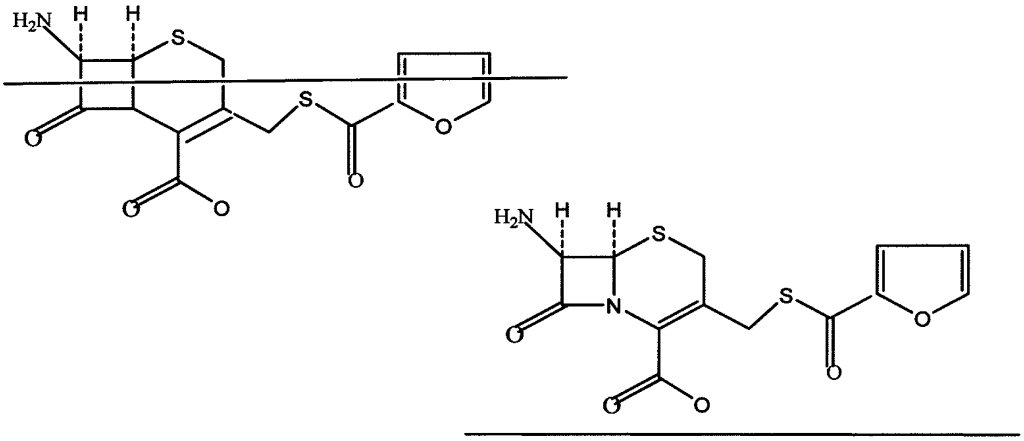


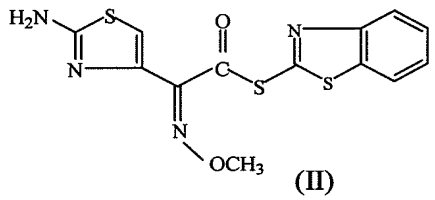
(II)

in an inert organic solvent (dichloromethane) in the presence of an organic base (triethyl amine) at ambient temperature (15-30°C), the methods had the following disadvantages, which are undesirable for any commercial process. These are,

Page 6, replace the formula at paragraph [0039] with:

An attempt by the present inventors to extend the method described in US Patent No. 5,026,843 for synthesis of ceftiofur or ceftiofur sodium comprising reaction of [2-(2-aminothiazol-4-yl)]-2-methoxyimino acetic acid-2-benzothiazolyl thioester (MAEM) of formula (II) with 7-amino-3-thiofuroylmethyl-3-cephalosporanic acid of formula (III),



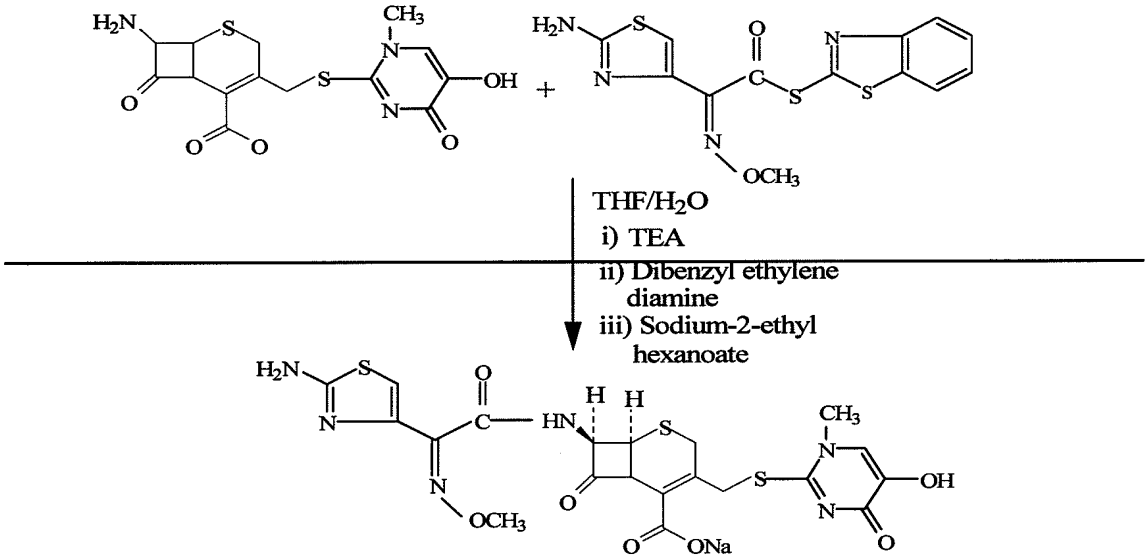


(II)

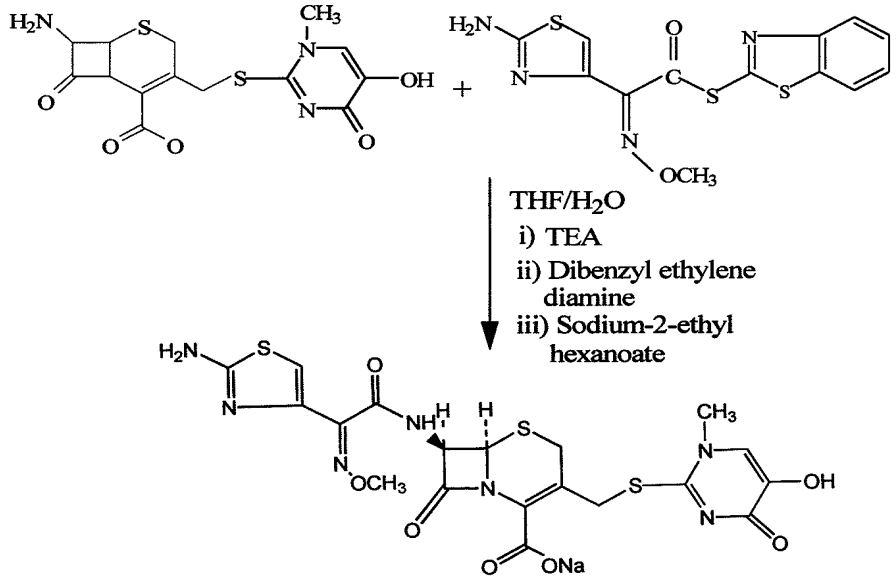
in a medium consisting of water and a water-miscible organic solvent disclosed in the said patent like tetrahydrofuran and N,N-dimethylacetamide, was however, not satisfactory and was found to give the product i. e. ceftiofur (I) associated with impurities in the level of 5-10% depending on the water-miscible organic solvent used. The product obtained was a sticky solid adhering to the sides of the reaction vessel, rendering its isolation as a solid very difficult.

Page 6, replace Scheme IV with:

Scheme IV: Mehtod for preparation of ceftriaxone sodium as disclosed in US Patent No. 5,026,843 B1

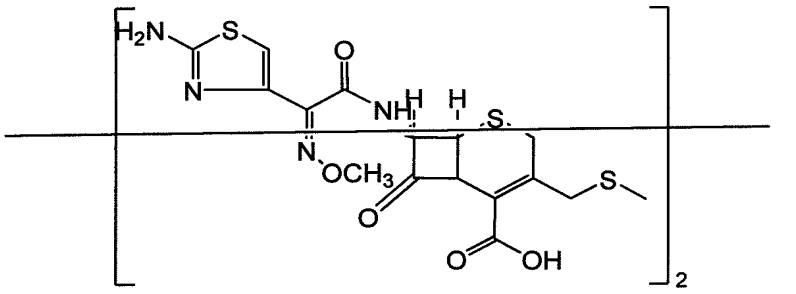


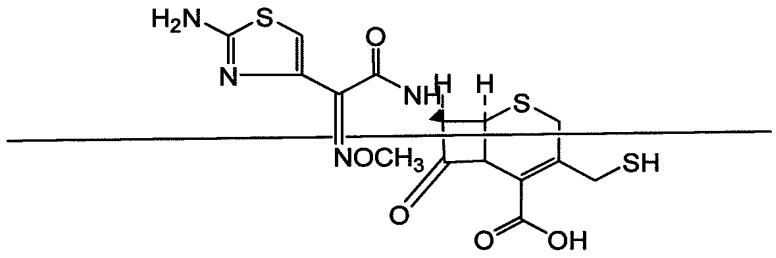
Scheme IV: Method for preparation of ceftriaxone sodium as disclosed in US Patent No. 5,026,843 B1

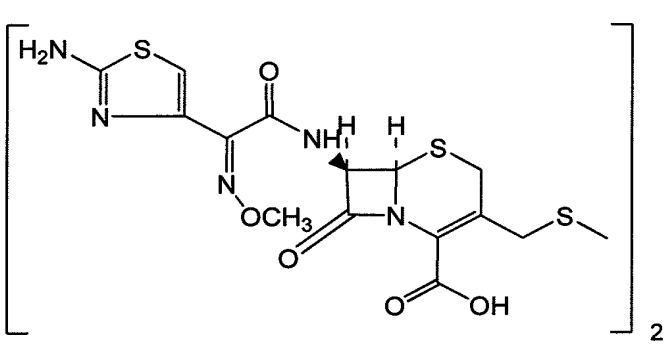


Page 7, replace paragraph [0043] with:

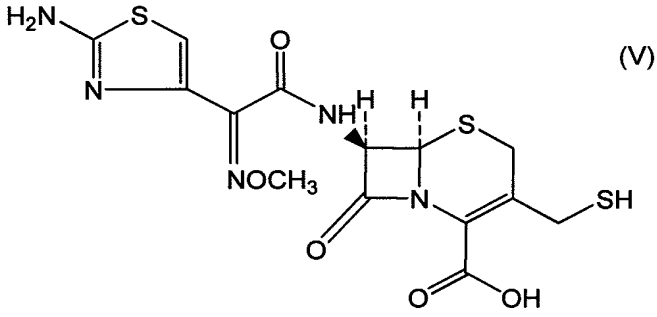
The structure of the impurities arising out of fission of the sulfur-carbonyl bond and dimerization are given herein below as compounds (IV) and (V) respectively.







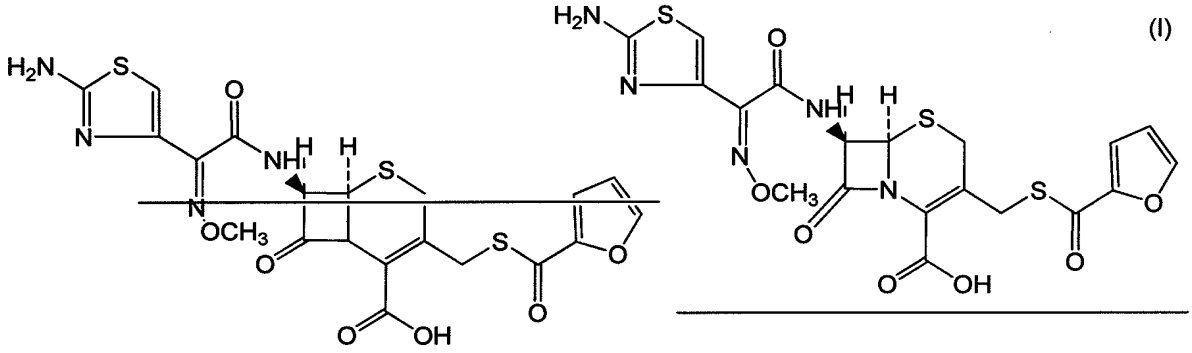
(IV)



(V)

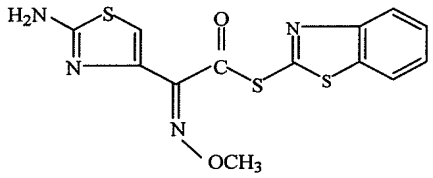
Page 8, replace the formula in paragraph [0062] with:

In one aspect, the present invention provides a simple, cost-effective method for manufacture of ceftiofur of formula (I),



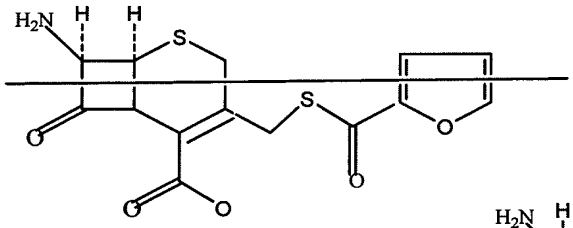
(I)

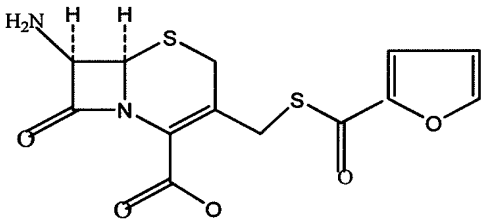
comprising reaction of [2-(2-aminothiazol-4-yl)]-2-methoxyimino acetic acid-2-benzothiazolyl ester of formula (II), and



(II)

7-amino-3-thiofuroylmethyl-3-cephalosporanic acid of formula (III),

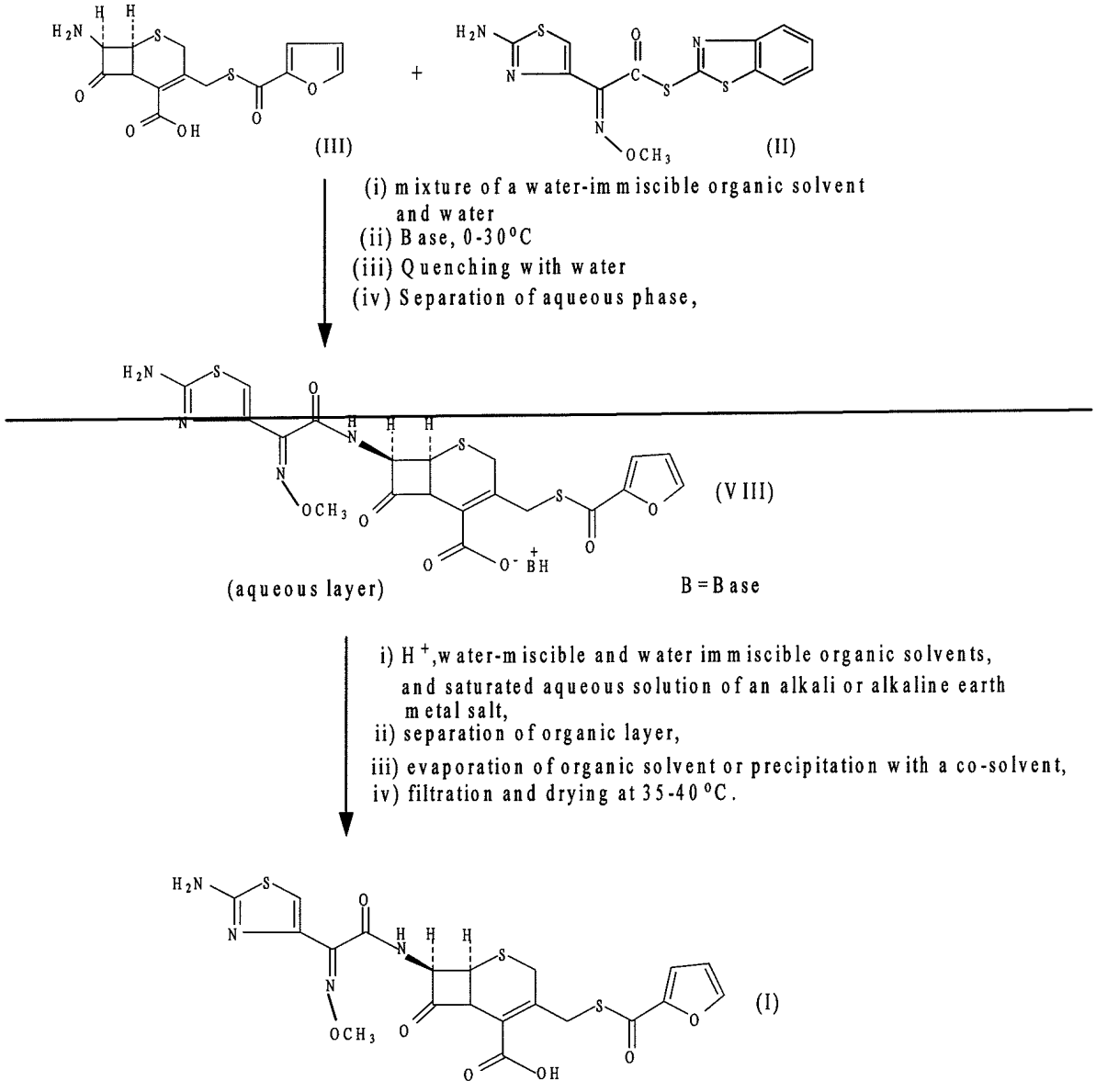




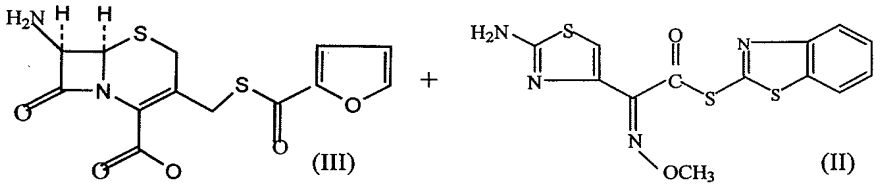
in the presence of a mixture comprising a water-immiscible inert organic solvent, and water and in the presence of a base and isolation to give ceftiofur of formula (I), in high purity and substantially free of impurities.

Pages 9 - 10, replace Scheme V with:

Scheme V Method of Manufacture of ceftiofur (I) as per the present invention

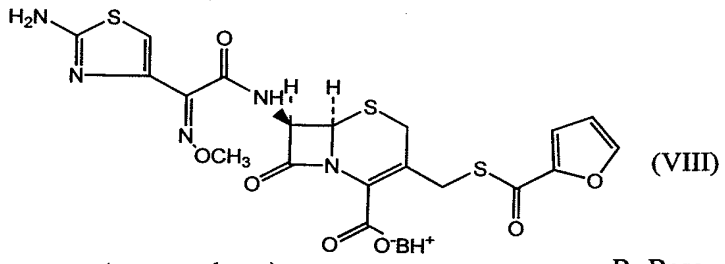


Scheme V Method of Manufacture of ceftiofur (I) as per the present invention



(III) (II)

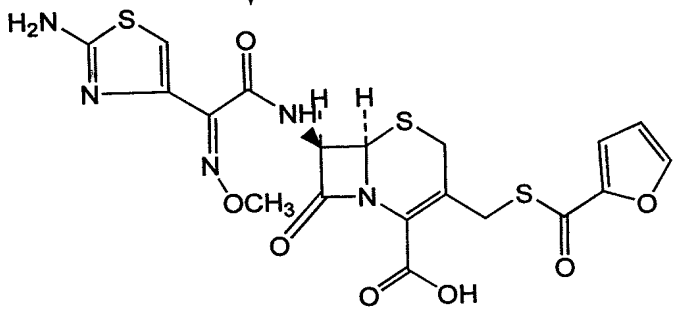
(i) mixture of a water-immiscible organic solvent and water
(ii) Base, 0-30°C
(iii) Quenching with water
(iv) Separation of aqueous phase,



(VIII)

(aqueous layer) B=Base

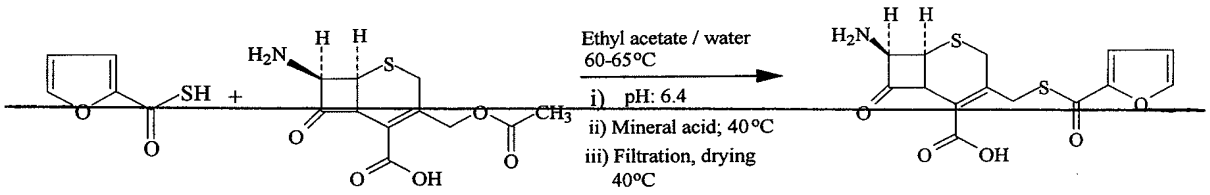
i) H^+,water-miscible and water immiscible organic solvents, and saturated aqueous solution of an alkali or alkaline earth metal salt,
ii) separation of organic layer,
iii) evaporation of organic solvent or precipitation with a co-solvent,
iv) filtration and drying at 35-40°C.



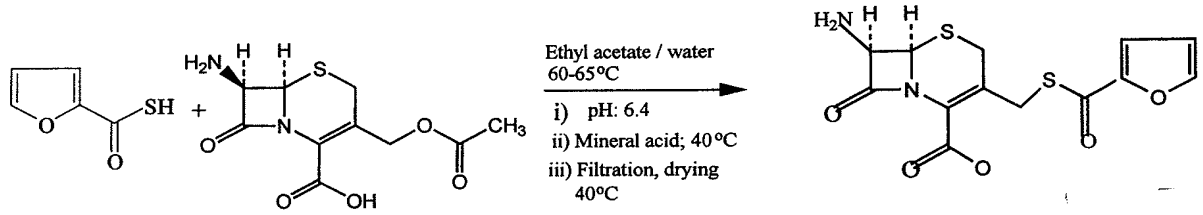
(I)

Page 10, replace the formula at paragraph [0068] with:

The starting materials required are prepared by known methods. 7-Amino-3-thiomethyl furoyl–3-cephem-4-carboxylic acid of formula (III) can be prepared by the method disclosed in US Patent No. 4,937,330; comprising reaction of thiofuroic acid of formula (VI) with 7-amino cephalosporanic acid of formula (VII) at pH 6.4 and temperature of 65°C in a mixture of water and an inert solvent such as ethyl acetate.



(VI) (VII) (III)



(VI) (VII) (III)

Page 11, replace paragraph [0080] with:

7-amino-3-thiofuroylmethyl-3-cephalosporanic acid of formula (III) on addition of an organic base is converted to its alkyl ammonium salt (III^2), which is soluble in the aqueous phase. The alkyl ammonium salt (III^2) reacts with the compound of formula (II), which is soluble in the inert water immiscible solvent, apparently at the interface between the aqueous and organic phase thereby minimizing / eliminating side reactions by a mechanism which has not been clearly understood and facilitating higher conversion with lower impurity formation.